the food upon the stomach itself. According to the experiments reported, there are some foods which contain substances capable of acting chemically upon the mucous membrane and arousing a flow of gastric juice, probably by a nervous reflex; such foods are the meats, meat extracts, milk, gelatin, and water. Other foods, such as bread or white of eggs, do not possess this power. If introduced into the stomach through a fistula without the animal's knowledge so as not to arouse a psychical

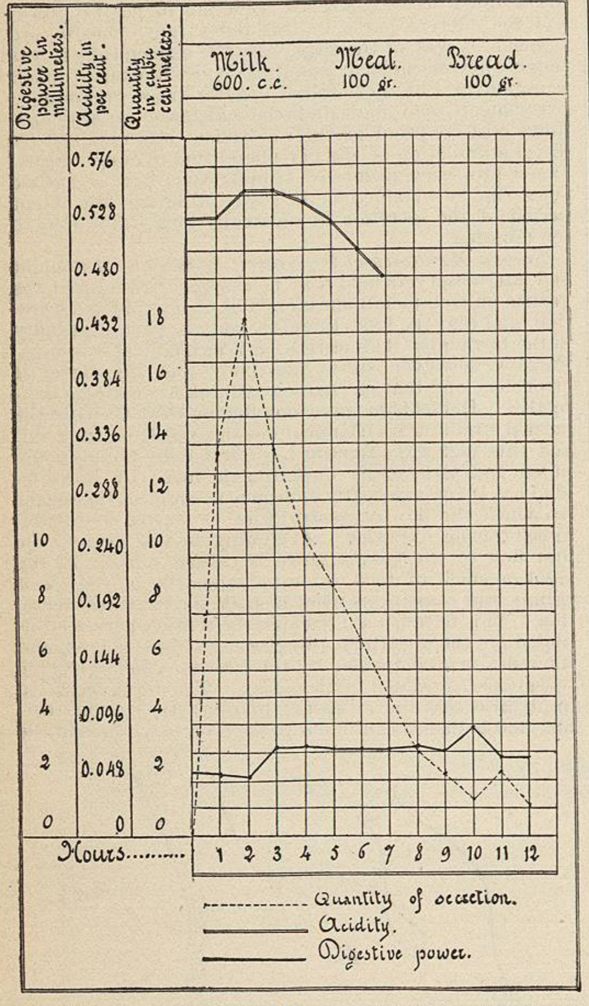

FIG. 4169.—Curve showing the Flow and Composition of the Gastric Secretion in a Dog Fed upon a Mixed Diet. (Khigine.)

secretion, they remain undigested. If, however, these foods are digested for a time they then acquire the power of stimulating a flow of gastric juice. Under the normal conditions of eating, such foods would first start a psychical secretion, and after they had begun to be digested by this secretion the flow would be maintained by the chemical stimuli developed from them in the process of digestion. These chemical stimuli upon which the flow of gastric juice depends mainly, which are present already formed in some foods and are developed in others by digestion, Pawlow groups under the general designation of secretogogues. He has not been able so far to ascertain their chemical nature. The dietetic value of meat extracts seems to lie largely in the fact that they contain much of these secretogogues and thereby favor the digestion of other foods.

Curve of Secretion and its Variation with the Character of the Food.—In its general features the curve of gastric secretion, so far as its quantity is concerned, resembles that of the pancreatic juice. The flow begins promptly after the act of eating, increases somewhat rapidly to a maximum, which in dogs fed on a mixed diet is reached at about the second hour, and then falls slowly toward zero as the stomach is emptied. The composition of the secretion during this period varies somewhat, the first flow being relatively weak in the two important constituents hydrochloric acid and pepsin. The illustration (Fig. 4169) gives an example of the way in which the secretion varies in a dog fed upon a mixed diet. Pawlow states that in a general way the quantity of secretion varies with the amount of food, a relation which is easily understood when we remember that the food itself supplies the stimulus for the secretion. The same worker has given some proof that the composition of the secretion is related to the composition of the food, and that it may be possible, when the relation has been more completely investigated, so to modify the food as to increase one or the other of its important constituents.

Histological Changes during Secretion.—The gastric glands in the cardiac end of the stomach contain two types of cells, the chief cells, and the cover or border cells. The latter vary in number in different regions, but in most cases form a discontinuous layer along the length of the tubes, and in the pyloric region they are lacking entirely. Histological and experimental evidence indicates that the chief cells are responsible for the secretion of the enzymes of the juice. During the resting stage these cells are filled with zymogen granules which disappear to a greater or less extent during active digestion. In accordance with this histological fact it is found that aqueous extracts of the mucous membrane in the resting stage may contain but little active pepsin or rennin, but that if this extract or the mucous membrane before extraction is treated with certain reagents such as dilute acids, an abundant yield of enzyme is obtained. In normal secretion the presence of the hydrochloric acid is sufficient in itself to convert the zymogen to enzyme, so that in the normal gastric juice no zymogen or proferment is found. With regard to the enzymes, therefore, we may assume that, as in the other digestive glands, they are formed within the cells as a result of their metabolism, that they are stored during rest as zymogen granules, and that, during or immediately subsequent to their secretion, the zymogen is changed to the active enzyme. With regard to the secretion of the acid prevalent theories are much less satisfactory.

Origin of the Hydrochloric Acid.—It is not known definitely which of the two cells found in the gastric tubules gives rise to the hydrochloric acid. The fact that the pyloric glands do not contain border cells and that their secretion is alkaline instead of acid suggests the view that these border cells are concerned in the formation of the acid, hence they are sometimes designated as oxyntic cells. No direct proof, however, has been furnished to show that these cells have anything to do with the production of the hydrochloric acid. On the chemical side also the mode of origin of the acid is still obscure. In general, it is believed that the hydrochloric acid must arise ultimately from the chlorides, especially the sodium chloride of the blood, and, according to one hypothesis, the acid is formed by a reaction between the chlorides and the phosphates of the blood according to the formula $NaH_2PO_4 + NaCl = Na_2HPO_4 + HCl$, the reaction being effected in some way through the activity of the gland cells. Another hypothesis is that the chlorides are decomposed by the mass action of the CO_2 formed in the metabolism of the gland tissue, and that the reaction is facilitated and the liberated base combined by an acid nucleoproteid known to exist in the gastric mucous membrane. Neither hypothesis helps us much to understand why the hydrochloric acid is formed only in this particular tissue and not elsewhere in the body. Acid indicators, such as acid fuchsin or a solution of ferric acetate and potassium ferrocyanide, show that the free acid is present only on the surface of the membrane and not within the substance of either the border cells or the chief cells. In

view of this result it has been supposed that the acid is not actually formed within the cells, but in the secretion after its discharge; or if formed within the cells, it is eliminated as rapidly as it is formed, so that there is no accumulation within the cell itself as in the case of the zymogen. In accordance with this hypothesis it has been suggested that the hydrochloric acid is actually formed outside the mucous membrane from the chlorides of the stomach contents. This view assumes that the mucous membrane is impermeable to the chlorine ions, but permeable to the hydrogen ions, and that the latter passing through the mucous membrane from the blood, combine with the chlorine of the dissociated chlorides of the stomach contents. The hypothesis can scarcely be considered a probable one, since an abundant secretion of acid juice may be obtained by stimulation of the vagus nerve or in the isolated fundic sac when the stomach is entirely empty. Nor does the hypothesis help us to understand at all the part taken by the secretory cells. We must, in fact, confine ourselves at present to the general statement that the chlorine of the hydrochloric acid is derived ultimately from the chlorides of the blood.

SECRETION OF THE SMALL INTESTINES—THE SUCCUS ENTERICUS.—Although there is no question that the cells of the small intestine form enzymes which take an active part in the digestion of the food, there is some doubt whether these substances are actually discharged in a liquid secretion upon the inner surface of the intestine. Some mucus is formed and secreted by the epithelial cells, particularly those of the large intestine, but this mucus is not known to have any digestive action of a chemical nature. To ascertain whether a liquid secretion other than the mucus is formed in the small intestine, recourse has been had usually to experiments with a Thiry-Vella fistula. In this operation a loop of the intestines is isolated and the two ends are sutured into the skin of the abdominal wall, giving thus a portion of the intestine whose contents can be examined without possibility of contamination from the food or from the secretions of the pancreas or liver. Experiments of this kind agree in showing that an alkaline liquid forms in the loops, and indeed more abundantly in loops from the lower than in those from the upper portions of the small intestines. From experiments of this kind Pregl estimates that as much as three litres may be secreted in twenty-four hours from the entire intestine. The estimate must be received, however, with caution. Most observers agree that this liquid has no digestive action on proteids, but may contain an amylolytic enzyme. Extracts of the walls of the small intestine, on the contrary, give solutions that contain four or possibly five important enzymes. There are, first, the essential group of sugar-splitting enzymes capable of converting the disaccharides to the monosaccharides, namely, maltase which converts maltose to dextrose, invertase which converts cane sugar to dextrose and levulose, and possibly lactase which converts lactose to dextrose and galactose. In addition it has been shown recently by Cohnheim that these extracts contain a powerful proteid-splitting enzyme, erepsin, which splits the peptones and proteoses into simpler crystallizable substances—leucin, tyrosin, arginin, etc. Whether or not these enzymes are actually discharged into the intestines as a liquid secretion, they must be regarded as formed within the substance of the intestinal epithelial cells by a metabolism peculiar to these cells and analogous to the process of secretion in other glands. We must place the intestinal epithelium among the important digestive glands. Quite recently also the intestinal secretion from the upper part of the small intestine at least has been found to contain an enzyme-like substance, enterokinase, which, while it has no digestive action of its own, seems to be able to increase greatly the activity of the enzymes of the pancreatic juice. This effect is particularly marked in regard to the important proteolytic enzyme trypsin. Apparently this latter enzyme is secreted entirely in the form of a zymogen and can have no effect upon the food until it is "activated" by the enterokinase. We owe this important addition to our knowledge of intestinal digestion to Schepowalnikow, working under Pawlow's directions. This work has since been confirmed by several observers, and it is claimed by Delezenne that the enterokinase can be obtained also from leucocytes and lymph glands, and in the small intestine is found most abundantly in the mucous membrane overlying the Peyer's patches.

SECRETION OF BILE.—As in the case of the other glands many efforts have been made to demonstrate the existence of secretory fibres to the liver controlling the flow of bile. The secretion of bile is continuous, the metabolic processes in the liver cells leading to its formation and discharge are in progress at all times, although the velocity of the flow varies. Experimentally the velocity of the secretion may be increased or decreased, but the variations are so strictly parallel to the concomitant changes in the circulation that a causal connection between the two is rendered most probable. Stimulation of the spinal cord or the splanchnic nerves diminishes the flow of bile in proportion as it causes a diminution in the blood supply. Section of the splanchnics, on the other hand, which causes a dilatation in the blood-vessels of the abdominal viscera, is said to increase the secretion of bile. The usual view, therefore, is that the velocity of secretion of the bile varies with the volume of the blood flow through the liver. This belief seems to imply that the secretory activity of the liver cells as regards the bile is controlled by the composition of the blood. With regard to the excretory products of the bile, the bile pigments, lecithin, and cholesterin, one can understand that the greater the quantity of blood flow through the organ the greater will be the excretion. It is more difficult to comprehend the relationship between the blood flow and the increased secretion of water, salts, and bile acids, and no satisfactory hypothesis has been suggested to explain the relationship.

Curve of the Secretion of Bile.—Owing to the ease with which a biliary fistula may be established in man as well as in the lower animals, our knowledge of the daily curve

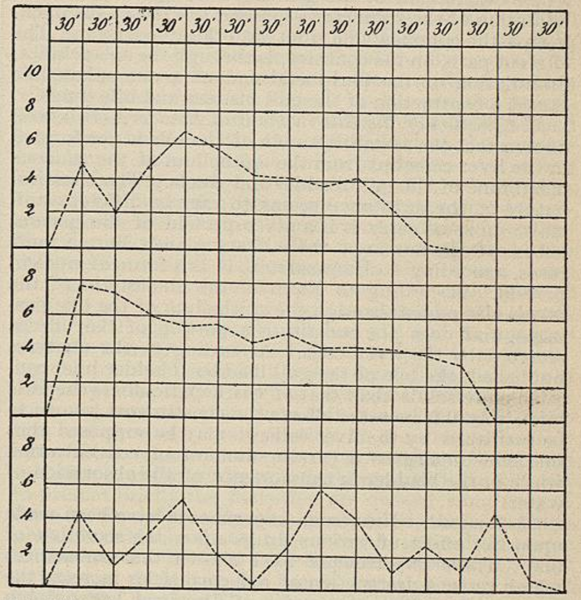

FIG. 4170.—Curves showing the Rapidity of Secretion of Bile into the Duodenum on (1) a diet of milk, upper curve; (2) a diet of meat, middle curve; (3) a diet of bread, lower curve. The divisions on the abscissa represent intervals of thirty minutes; the figures on the ordinates the volume of the secretion in cubic centimetres. (Bruno.)

of the secretion is fairly accurate. In man the quantity secreted varies between 500 and 800 c.c. in the course of a day, or taking into account the weight of the individual the secretion averages from 8 to 16 c.c. per day for each kilogram of body weight. Although the secretion is continuous, it shows a marked acceleration during the period of digestion between the third and the fifth hours after the ingestion of food, that is, during the period of maximal activity in the small intestine. Upon the general theory of secretion stated above, this increase in the secretion should be related to the greater blood flow through the liver at this period, and the altered composition of the blood following absorption of the digested products. Absorption, which is at its maximum during this time, must lead to a greatly increased metabolism in the liver cells, and the augmented secretion of bile is one expression of this increased activity. Although the secretion is continuous, the actual injection of bile into the duodenum through the common bile duct is intermittent in those animals which possess a gall bladder. The secretion in such animals is stored in the gall bladder, and by means of a definite nervous mechanism this reservoir is emptied at intervals during the course of digestion.

Ejection of Bile into the Duodenum.—The mechanism by which the bile is emptied into the intestine does not seem to have been investigated by recent observers. According to Bruno, the ejection through the common bile duct is dependent upon the passage of chyme from the stomach into the intestine, and varies with the character of the food. As long as the stomach is empty no bile is found in the duodenum. The chyme therefore must contain substances which, acting upon the sensory surface of the duodenum, lead to a reflex contraction of the gall bladder. Bruno thinks that the digested proteids (proteoses and peptones) and fats furnish the efficient stimuli. Acids, alkalies, and starches were found to be ineffective. There seem to be no data regarding the frequency of occurrence of these contractions during digestion or the action of stimuli other than the chyme. The nervous mechanism involved in this reflex has been studied by Doyon and by Oddi. It appears from their work that the afferent fibres for the reflex run in the vagi, since stimulation of the central end of a cut vagus causes a reflex contraction of the gall bladder together with an inhibition of the sphincter supposed to exist at the opening of the common bile duct into the duodenum. The efferent path, on the contrary, is through the splanchnics. Stimulation of the peripheral end of a cut splanchnic causes a contraction of the gall bladder and bile ducts.

Modification of the Bile in the Gall Bladder.—It is well known that the so-called mucin of the bile is not formed in the liver cells but from the epithelium of the mucous membrane of the gall bladder and ducts. The chemical nature of the substance seems to vary in different animals; in some cases it is a glyco-proteid of the general nature of the mucin of the salivary glands, but in most cases, according to Hammarsten, it is a form of nucleo-proteid. According to Naunyn, the cholesterin of the bile is also added through the epithelium of the bile passages, and does not constitute a portion of the bile as secreted by the liver cells. According to the analyses published, the bile of the gall bladder (bladder bile) contains more solids than that of the hepatic ducts (hepatic bile). As this increase affects the constituents known to be furnished by the liver cells, it may be supposed that the bile undergoes a certain amount of concentration while in the bladder in consequence of the absorption of water.

Cholagogues.—Numerous experiments have been made upon the effect of various drugs upon the secretion of bile. These experiments have shown that substances which cause a destruction of red corpuscles increase the flow of bile. Direct injection of dissolved hæmoglobin into the circulation has the same effect. The increase in the secretion in such cases is said to be transient. The substance that has the most marked and prolonged effect upon the secretion of bile is bile itself. Bile fed to an animal or injected into the circulation accelerates the secretion of bile, and the same effect may be obtained by using solutions of the bile acids alone. Since the so-called bile acids have a distinct hæmolytic action it might be supposed at first that their effect as cholagogues is due to this action on the red corpuscles; but their effect is so much greater than that of other hæmolytic agents that we must believe that they exert a specific stimulating effect upon the liver cells. Many other substances seem to occasion a slight increase in the flow of bile, but no direct cholagogue of importance has been discovered other than the bile salts themselves. Perhaps an exception will be found to this last statement when further investigations are made upon the physiological action of the secretin formed in the duodenum and jejunum. Attention is called to this substance under the head of pancreatic secretion, and there is some indication that it may play a part as a normal chemical stimulus in the secretion of bile. At the present writing no more precise statement can be made.

Secretion of the Kidney.—None of the secretions of the body has been studied with more care than that of the kidney. The especial interest which this secretion possesses for pharmacology and internal medicine as well as for physiology accounts in large part for the attention it has received. In addition it has seemed to offer the best opportunity for testing one of the fundamental questions of secretion, namely, the extent to which the physical processes of filtration, diffusion, and osmosis participate in the act of secretion. Most of the discussion on this point has been along the lines of the two main theories of urinary secretion which have been under discussion now for many years. One theory, proposed first substantially by Bowman and afterward supported vigorously in a modified form by Heidenhain, holds that the water and salts of the urine are actively secreted by the epithelium of the capsule surrounding the glomerulus, while the urea and the other specific organic constituents of the urine are secreted together with some water by the epithelium of the convoluted tubules. The other theory we owe to Ludwig. According to him all the constituents of the urine are formed by filtration through the glomerulus. The two layers of epithelium through which this filtration occurs, the capillary or vascular, and the glomerular epithelium, act simply as a membrane through which the constituents of the urine are filtered off from the blood by the excess of pressure in the blood capillaries. The urine so formed is very dilute, and as it passes along the convoluted tubules it becomes concentrated by absorption. In both theories a difference of function is supposed between the capsule and the convoluted tubule. It will be convenient to discuss the functions of these two parts separately.

Function of the Glomerulus.—The arrangement of the glomerulus and the capsule presents a structure peculiar to the kidney and suggestive of a special purpose. The glomerulus is a knot of capillary vessels which do not form a plexus but rather a rete mirabile with a single afferent and a smaller efferent vessel. For physical reasons the blood in passing through the glomerulus suffers a diminution in velocity, on account of the sudden increase in the width of the stream bed, and yet maintains a high hydrostatic pressure on account of the resistance offered by the narrow efferent vessel and the capillary plexus with which it connects. Moreover, there are no lymph spaces round the glomerulus. The epithelium of the blood capillaries is directly adherent to the epithelium of the capsule into which the glomerulus is inserted, so that the cavity of the capillaries is separated from that of the uriniferous tubules by a double layer of endothelial cells. The arrangement suggests a filtering mechanism, and Ludwig's theory supposes that it acts in this way for all of the constituents of the urine. Bowman's theory supposes that only the water and salts are formed here, and Heidenhain, moreover, has given reasons for believing that the water is not formed by mechanical processes, but by an active secretory process on the part of the glomerular epithelium. If attention is paid only to the water and salts it is evident that if Ludwig's theory is correct the pressure tending to force them through the epithelium may be expressed by the formula $P - p$, in which P represents the pressure in the glomerular capillaries and p the pressure of the urine in the capsular end

of the tubule. According to this theory, the amount of urine formed should vary directly with P and inversely with p. It is obvious that the factor P may be increased by raising arterial pressure in the renal arteries or by obstructing the flow in the renal veins, and, according to theory, each change should cause an increased flow of urine. Experiments of this kind have been made. It has been found that raising arterial pressure in the kidney arteries does increase the flow of urine, and vice versa. However, it must be borne in mind that this relationship holds only when the pressure in the glomerular capillaries varies in the same direction as in the renal arteries. All experimental variations which may be safely assumed to raise the pressure in the glomerular capillaries are followed by a greater flow of urine. The reverse experiment, however, of raising P by blocking the venous outflow fails entirely to support the theory. When the renal veins are compressed the capillary pressure in the glomeruli must be increased, and if the veins are blocked entirely, we may suppose that the capillary pressure is raised to the level of that of the renal arteries. In such experiments, however, the flow of urine is diminished instead of being increased, and indeed may be stopped altogether when the veins are completely blocked. The adherents of the Ludwig theory have attempted to explain this unfavorable result by assuming that the swollen interlobular veins press upon and block the uriniferous tubules.

According to the antagonistic theory of Heidenhain, blocking the veins suppresses the secretory activity of the glomerular epithelium by depriving it of oxygen and the chance for removal of CO_2, and thus producing local asphyxia. The latter explanation seems the simpler of the two, and it is very strongly supported by the opposite experiment of clamping the renal artery. When this is done the blood-flow through the kidney ceases and the secretion of urine also stops as would be expected. But when after a few minutes' closure the artery is unclamped the secretion is not restored with the return of the circulation. On the contrary, a long time (as much as an hour or more) may elapse before the secretion begins. This fact is quite in harmony with the Heidenhain theory, since complete removal of their blood supply might well result in a long-continued injury to the delicate epithelial cells. On the mechanical theory, however, we should expect the contrary. Injury to the cells should be followed by greater permeability and an increased filtration, as is found to be the case with the production of lymph. These two experiments, blocking the renal artery and the renal vein, seem at present to discredit the filtration theory and to support the secretion theory. If we accept this latter theory it may be asked how it agrees with the experiments mentioned above upon the variations in capillary pressure brought about otherwise than by obstructing the venous outflow. Heidenhain has emphasized the fact that all of these experiments involve not only a variation in capillary pressure, but also in the blood flow, and that it is open to us to suppose that the effect upon the secretion of urine is dependent upon the rate of flow rather than upon the capillary pressure. If we adopt this explanation we are led again to the secretion hypothesis, since mere rate of flow should not influence filtration, but should affect secretion, since it would alter the composition of the blood flowing through the glomeruli and also the supply of oxygen and carbon dioxide. An important fact, which seems at first sight to show the influence of pressure, is that when general arterial pressure falls below a certain point, about 40 mm. of mercury, the secretion of urine ceases altogether. Such a condition may be brought about by surgical shock, by hemorrhage, or by section of the spinal cord in the cervical or thoracic region. But here again the great vascular dilatation causing this fall of pressure is associated with a feeble circulation, and the effect upon the kidney secretion may well be due to this latter factor.

In addition to varying the factor P in the formula given above, it is possible also to increase the factor p. Normally the pressure of the urine in the capsule must be very low owing to the fact that the secretion drains away as rapidly as it is formed. If the ureter is occluded, however, the pressure of the urine will increase, and the filtration pressure $P - p$ will diminish. When this experiment is performed and the pressure in the ureter is measured by a manometer, it is found to rise to 50 or 60 mm. of mercury and then to remain stationary. This fact might be explained by supposing that when $p = P$ the secretion stops on account of the failure of the filtration pressure. Little weight, however, can be given to this argument, since it is quite possible that under these conditions the urine may still continue to form, but is reabsorbed under the high tension reached. The experiment simply serves to show the secretion pressure of the urine, and the fact that this pressure rises as high as 50 to 60 mm. mercury, while the fact that the capillary pressure is probably somewhat lower would rather serve as an argument against the filtration theory. Exact figures, however, regarding the capillary pressure in the kidney cannot be obtained, so that the experiment on the whole gives us no satisfactory information regarding the theory of secretion. Dreser has used a different argument to prove that the production of the water involves the performance of work on the part of the epithelial cells. He points out that in some conditions, *e.g.*, after drinking beer, the urine may be very dilute, as shown by the fact that its freezing point may be only 0.18° C. or 0.16° C. below that of pure water, that is, $\Delta = -0.18°$ C. or $-0.16°$ C. Since blood serum has $\Delta = -0.56°$ C. the difference in concentration between the blood and the urine in such a case of extreme dilution shows an osmotic pressure in favor of the blood equivalent to $\Delta = -0.4°$ C. Measured in mechanical units this would indicate an osmotic pressure of 49.08 metres of water tending to drive the water from the uriniferous tubules into the blood, whereas the filtration pressure driving the water in the other direction could not at a maximum exceed 2.72 metres of water. Evidently if this argument is just, the elimination of the water takes place against a strong opposing osmotic pressure, and the energy necessary for its secretion can be referred only to the activity of the epithelial cells.

Function of the Convoluted Tubules.—By convoluted tubule is meant that portion of the uriniferous tubule which extends from the capsule to the straight or collecting tubes. Its epithelium varies, but is distinguished in general from the flat, thin epithelium of the capsule by a larger amount of granular protoplasm. According to the Ludwig theory, this portion of the tubule functions as an absorption membrane and serves thus to concentrate the dilute urine filtered through the glomerulus. The fact that the urine is often more concentrated than the blood proves that this absorption, if it occurs, is not due to simple hydro-diffusion, and later adherents of this theory have been obliged to abandon the simple physical theory proposed by Ludwig and to suppose that the absorption effected by these cells is a physiological process dependent upon their living structure and properties. The Bowman-Heidenhain theory, on the contrary, assumes that these cells are secretory in function and serve for the excretion of the urea, uric acid, etc. With regard to the absorption theory it may be said that positive evidence is lacking, and it is difficult to present briefly the facts that are quoted from time to time in its favor. On the other hand, there is much probable evidence that the secretory hypothesis is nearer to the truth. This evidence may be summarized briefly as follows: 1. It is stated that if the ureters are ligated in birds the urates will be found deposited in the uriniferous tubules, but never at the capsular end. 2. Heidenhain has given proof that the convoluted tubules are capable of excreting indigo-carmine after this substance is injected into the blood. His experiment consisted essentially in injecting the material into the blood after dividing the cord so as to reduce the rapidity of secretion. After a certain interval the kidney was removed and irrigated with alcohol to precipitate the indigo-carmine *in situ* in the organ. Microscopic examination showed that after this treatment the granules of the indigo-carmine are found in the convoluted tubules, but not in the capsules round the glomeruli. 3. Several observers (Van der Stricht, Disse, Trambasti, Gurwitsch) have described microscopic appearances in the cells lining the tubules indicative of an active secretion. They picture the formation of vesicles in the cells and appearances which indicate the discharge of these vesicles into the cavity of the tubules. 4. Nussbaum made use of the fact that in the frog the glomeruli are supplied by branches of the renal artery, while the rest of the tubes are supplied by the renal portal vein. He stated that if the renal artery is ligated the glomeruli are deprived completely of blood, and that as a result the flow of urine ceases. If under these conditions urea is injected into the circulation it is excreted together with some water, thus proving the secretory activity of the tubules with regard to urea. Later experiments by Adami and by Beddard have thrown doubt upon this otherwise crucial experiment. Adami claims that ligature of the renal arteries does not shut off completely the glomerular circulation, while Beddard, although he corroborates Nussbaum in the point that complete occlusion of the renal arteries suspends entirely the secretion of urine, finds that under these conditions injection of urea into the circulation is not followed by a secretion. 5. Dreser has shown that the acidity of the urine is due to an action of the epithelium of the tubules. If an acid indicator, such as acid fuchsin, is injected into the dorsal lymph sac of a frog, and an hour or so later the kidneys are examined, it will be found that the convoluted tubules are colored red, while the capsular end is colorless, indicating that the secretion at that point has an alkaline reaction. The experiment shows that the acid phosphate of the urine is produced in the convoluted tubules. The simplest explanation is that it is formed by a secretory activity of the epithelial cells, although one may adopt the less probable view that the cells produce the acid phosphates by a selective absorption of alkaline salts. On the whole it must be admitted that the weight of evidence is in favor of the Bowman-Heidenhain theory of secretion, and it remains for future investigations to explain more definitely what is meant by the obscure term, secretory activity.

Under pathological conditions it has been shown satisfactorily that albumin and sugar which may be present in the urine are secreted or eliminated at the glomerular end of the tubule.

Influence of the Nervous System on the Secretion of Urine.—Although Berkley states that terminal fibrils of the nerves distributed to the kidney may be traced to the epithelial cells of the convoluted tubules, the physiological evidence at present is opposed to the existence of secretory nerve fibres. The kidney receives a rich nervous supply by way of the sympathetic, but experiments indicate that these fibres are vaso-motor in function. Both vaso-constrictor and vaso-dilator fibres have been described, and inasmuch as the secretion of urine varies directly with the rapidity and volume of the blood flow, it follows that these vaso-motor fibres must exercise normally an important regulatory influence upon the amount of secretion.

Action of Diuretics.—An important side of the theories of secretion of urine is their application to the action of diuretics. Water, various soluble substances, such as salts, urea, and dextrose, and certain special drugs, such as caffein or digitalis, exert a diuretic action on the kidneys. Much experimental work has been done to ascertain whether the action of these substances can be explained mechanically by their influence on the blood flow or the blood pressure in the kidney capillaries, or whether it is necessary to fall back upon a specific stimulating effect exerted by them upon the epithelial cells of the tubules. Adherents of the original Ludwig theory are forced to explain their action by the effect they produce upon the pressure in the kidney capillaries, and indeed it has been shown with reference to the saline diuretics that their effect upon the secretion is in proportion to the osmotic pressure they exert. It has been suggested, therefore, that the action of these diuretics lies in the fact that they attract water from the tissues into the blood and thus cause a condition of hydræmic plethora. But whether the elimination of this excess of water is due to filtration or to an active secretion by the glomerular epithelium simply revives the discussion that has been presented briefly above. Most observers find that the vascular changes in the kidney, particularly after the administration of caffein and digitalis, do not explain satisfactorily the phenomenon of diuresis, and although it is necessary to admit that the diuretics, or some of them, act in part by the changes which they cause in the circulation in the kidney, those who adopt the Bowman-Heidenhain theory assume usually that these substances exert also a direct stimulating action on the secretory cells.

Secretion of the Sebaceous Glands.—Practically nothing is known of the mechanism of secretion of these glands beyond the results furnished by histological examination. It is believed that the secretion is formed not by a liquid discharge from the cells, but by the casting off of the cells themselves. The cells upon the basement membrane multiply, and the daughter cells are displaced toward the lumen of the gland. Gradually these latter cells disintegrate, and their débris forms the thick, oily secretion.

Secretion of the Sweat Glands.—The secretion of sweat is important, partly because it helps to regulate the water contents of the body, but mainly because it is an effective means of controlling the body temperature. In accordance with these regulative functions we find that the formation of sweat is governed by the central nervous system, by means of which a reflex adaptation of the process to the needs of the body is made possible. Definite experimental proof of the existence of sweat nerves was obtained first by Goltz. He showed that electrical stimulation of the peripheral end of the divided sciatic in dogs or cats causes the formation of visible drops of sweat on the balls of the feet. This result has since been confirmed for other parts of the body, and it has been shown that the sweat nerve fibres take much the same course anatomically as the vaso-motor fibres. They take origin in the cord or the medulla, pass over to the sympathetic ganglia where they end round the sympathetic nerve cells. Thence their course is continued by a sympathetic neurone, so that they reach their destination probably as non-medullated fibres. Their course for different regions of the body is known with a fair degree of exactness. All the evidence that we have indicates that the sweat glands, like the salivary glands, do not secrete normally except under the influence of these secretory fibres. Ordinary profuse sweating due to a high external temperature must be explained as a reflex act. The high temperature stimulates sensory nerves in the skin, and the impulses thus generated are transmitted to the cord and returned to the sweat glands by the efferent sweat fibres. Attempts have been made to ascertain whether the general activity of these sweat fibres is controlled like that of the vaso-constrictors by a medullary nerve centre. The work done is not conclusive, but it seems to indicate that the reflex centres for the system are found in different regions of the brain and cord. In all probability the nuclei of origin of the sweat fibres for each skin area constitute the sweat centre for that region. These nuclei or centres may be stimulated reflexly by incoming impulses from the skin or from the higher nerve centres, or they may be acted upon by changes in the composition of the blood as is shown by the effect of dyspnœa and certain drugs. Atropin and pilocarpin exert their well-known antagonistic influence in the sweat secretion, the latter causing a flow of sweat and the former inhibiting it. As in the case of other glands, the action of these drugs is supposed to be peripheral, pilocarpin stimulating the endings of the sweat fibres, and atropin paralyzing them. Nicotin also in proper doses suspends the secretion of sweat, and it is probable that this alkaloid acts upon the connection between the spinal or pre-ganglionic neurone and the sympathetic or post-ganglionic neurone.

Secretion of the Mammary Glands.—The development of these glands in connection with the processes of gestation and their functional activity for a variable period after the act of parturition, are the points of greatest physiological interest. It seems evident that the causal connection between the changes in the uterus and in the mammary gland must be established either through the central nervous system or through the blood. During the development of the fœtus sensory stimuli may be developed in the reproductive organs of the mother which act reflexly upon the mammary gland and stimulate its growth and secretion; or, on the other hand, the changes in the reproductive organs may result in the formation of an internal secretion, which being discharged into the blood, acts upon the tissue of the gland either directly or through the nervous system. The crucial experiment of destroying the nerve supply of the gland in a pregnant animal has given somewhat unsatisfactory results, but it seems to show that the development and functional activity of the gland proceed as under normal conditions, although the quantity of milk produced is less. As far as it goes this evidence indicates that the bond of connection is furnished by the blood rather than by the nervous system, and we may adopt provisionally the hypothesis of an internal secretion. Assuming that this hypothesis is correct, it still remains possible, of course, that the activity of the gland in lactation may be regulated by extrinsic nerves. Many facts speak for this possibility. It is known, for instance, that in women during lactation the flow of milk is influenced by emotional conditions, and, on the other hand, histologists have described nerve terminations round the gland cells which look like secretory nerve fibres. The physiological evidence for secretory fibres is, however, quite meagre. Mironow in experiments upon goats has stated that stimulation of sensory nerves causes a diminution in the secretion, but that when the nervous connections of the gland are destroyed this reflex cannot be obtained. Röhrig finds that section of the inferior branch of the external spermatic increases the secretion, while stimulation of the same nerve causes a diminished secretion. These experiments might be regarded as proving the existence of inhibitory fibres to the gland, but it is equally, or indeed more probable, that the fibres in question are vaso-constrictors. The known influence of the central nervous system on the secretion of milk may therefore consist only in the control of the circulation in the gland by means of vaso-motor fibres as in the case of the secretion of urine.

Internal Secretions.

The term internal secretion seems to have been employed first by Claude Bernard, but the essential idea conveyed by it, namely, a secretion discharged into the blood or lymph, had long been entertained in connection with the so-called ductless glands, such as the thyroid. About 1889 the term and the idea implied by it were emphasized by Brown-Séquard in connection with work upon testicular extracts. This author suggested that not only the glands but all tissues may have internal secretions of greater or less importance in the general nutrition of the body. This extension of the original conception was not justified by subsequent experiments and to-day we must limit the use of the term to the distinctly glandular bodies. Experience has shown, however, that not only the ductless glands but some at least of the typical glands with well-defined ducts may produce internal secretions. There is no *a priori* way of determining whether or not a glandular structure produces an internal secretion. The matter must be decided by experiment and observation.

Internal Secretion of the Thyroid Tissues.—Under the term thyroid tissue we may include the thyroid bodies, the accessory thyroids which have a similar, indeed identical structure, and the parathyroids whose structure is peculiar, but whose function seems to be closely related to that of the thyroids. The history of the discovery of the functions of the thyroids, so far as we know them, is most interesting and illustrates admirably how experimental physiology may co-operate with experimental and clinical work in medicine and surgery. The early work indicated that removal of the thyroids is followed quickly by marked symptoms of disturbed metabolism, cachexia, muscular tremors and spasms which soon end in death. Later work has shown that a rapidly fatal result is obtained only when the operation removes all of the thyroid tissues, and that the characteristic symptoms and their duration before a fatal termination depend somewhat upon the species of animal used and its age. In human beings it is known that atrophy or loss of function in the thyroids leads to cretinism and myxœdema, and that these distressing conditions may be removed completely by feeding thyroid tissue to the patient. In the lower animals the precise results of removal of the thyroids proper and of the parathyroids are not yet clearly known. Upon many animals, dogs, cats, rabbits, rats, operations that remove both the thyroids and the parathyroids result in the rapid death of the animal with the symptoms of cachexia and muscular convulsions mentioned above. In the higher mammals (the monkeys, for instance), the symptoms are said to develop more slowly and to resemble more nearly the myxœdema of man. One observer claims that in those animals, such as dogs, in which the fatal result of thyroidectomy is most prompt, a distinction may be made between removal of the thyroids and removal of the parathyroids. Removal of the former causes a slowly developing malnutrition, a progressive cachexia whose fatal termination may be long deferred. Removal of the parathyroids, on the contrary, occasions more acute symptoms including muscular convulsions and a rapidly fatal result. This distinction needs, however, further confirmation before it can be accepted. It is stated also that the fatal outcome of complete thyroidectomy may be deferred or obviated completely by grafting a portion of the gland under the skin. These results upon man and the lower animals are usually explained upon the assumption that the thyroid tissues furnish an internal secretion which plays an important and indeed essential part in the metabolism of the body, particularly perhaps of the nervous system. There is histological evidence to show that the colloid material contained in the vesicles of the glands is emptied into the lymphatics and thence reaches the blood. On the other hand, it has been proved that the beneficial material in extracts of the glands is obtained from this same colloidal material. We may therefore regard this substance as a secretion which is discharged into the blood by way of the lymphatics. Bauman has succeeded in obtaining from the gland a peculiar organic compound containing iodine to the amount of nine per cent. of the dry weight. He designated this substance as iodothyrin and showed that in the gland it exists in combination with proteid. Inasmuch as the iodothyrin, when used upon animals or patients, has much the same beneficial effect as the crude thyroid extract, we must believe that it represents one at least of the essential constituents of the internal secretion. How it or other substances affect normally the metabolism of the body is not yet explained. We know only that complete loss of this substance is followed by a perverted metabolism and finally by death. There is much evidence to show that feeding thyroid extracts to normal individuals leads to an increase in physiological oxidations, hence its use in cases of obesity. This fact is a further indication of the influence of its secretion on normal metabolism, but the means by which it influences the nutrition of the cells cannot be determined without further work.

The Adrenal Bodies.—Brown-Séquard was the first to show that removal of these bodies in dogs is followed by the death of the animal within a day or two. Subsequent observers have confirmed this fundamental fact, and have shown that the symptoms preceding death are great muscular weakness, a loss of vascular tone, and a